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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/35, 31/365, 9/00, 9/20	A1	(11) International Publication Number: WO 99/15166 (43) International Publication Date: 1 April 1999 (01.04.99)
(21) International Application Number: PCT/EP98/05720 (22) International Filing Date: 4 September 1998 (04.09.98) (30) Priority Data: 9720228.7 23 September 1997 (23.09.97) GB 9810143.9 12 May 1998 (12.05.98) GB (71) Applicant (for GB only): PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). (71) Applicant (for all designated States except GB US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): HUATAN, Hiep [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). (74) Agents: HAYLES, James, Richard et al.; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PARASITICIDAL FORMULATIONS (57) Abstract The invention provides a solid implant comprising at least one parasitocidal compound having low aqueous solubility; and tableting excipients including a bulking agent. Implants according to the invention are convenient to administer and provide prolonged protection against parasites.		

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Parasiticial formulations

This invention relates to a solid implant containing a parasiticial compound having low aqueous solubility, which is particularly useful for administration to livestock such as cattle, pigs and sheep.

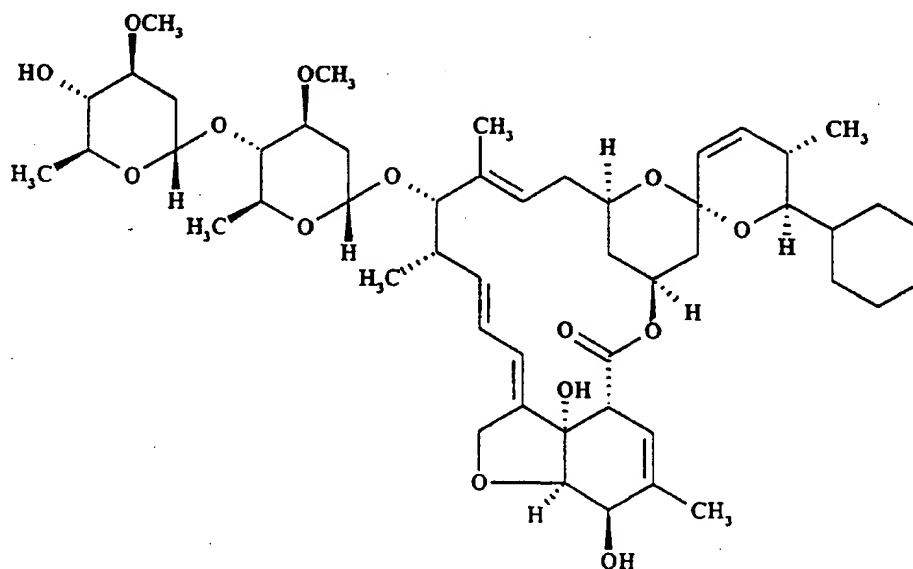
A number of potent macrocyclic parasiticial compounds are known, including the avermectins and milbemycins. UK Patent N° 1,573,955 discloses a family of avermectin compounds (including avermectins B1a and B1b) which are indicated as parasiticides.

10

22,23-Dihydroavermectin B1 (ivermectin, disclosed in EP 1689) is available commercially in an injectable formulation (sold as IVOMEC™). Ivermectin is a mixture of at least 80% 22,23-dihydroavermectin B1a (having a 25-sec butyl group) and not more than 20% of 22,23-dihydroavermectin B1b (having a 25-isopropyl group).

15

25-Cyclohexyl-avermectin B1 (doramectin, disclosed in EP 214731) has the following structure,



and is available commercially in an oil formulation for injection (sold as DECTOMAX™) for the treatment and prevention of internal and external parasite infestations in cattle. The oil formulation is described in European Patent N° 393890.

20

The milbemycins are similar in structure to the avermectins, except that they are unsubstituted at the 13-position.

Although formulations such as DECTOMAX™ have been successful, there is a need for
5 further formulations which are convenient to administer and which provide prolonged protection against parasites.

European Patent Application 240274 discloses the use of avermectins as growth promoting agents. European Patent Application 311195 discloses the use of avermectins in the
10 prevention of fescue toxicosis in grazing animals. In both documents, a subcutaneous implant is claimed, but no teaching is provided about how such an implant would be produced.

European Patent Application 473223 discloses a complex bioerodible implant in which
15 active agents such as anthelmintics are incorporated covalently into a chain backbone of a constituent polymer.

European Patent Application 537998 discloses a drug delivery device compounded of a polymeric matrix, a vehicle (which is a plasticizing solvent for the polymeric matrix) and a
20 drug. The drug may be an avermectin or a milbemycin, and the device is intended for topical delivery of drugs, such as a flea or tick collar for pets.

Thus, according to the present invention, there is provided a solid implant comprising at least one parasiticide compound having low aqueous solubility; and tableting excipients
25 including a bulking agent.

An important feature of the implants of the present invention is their simplicity. Preferably therefore, greater than 95% by weight of the implant is made up of parasiticide compound and tableting excipients, more preferably greater than 99% by weight.

Implants according to the invention may be implanted intramuscularly. Preferably however, they are implanted subcutaneously (i.e. into the fatty tissue directly below the skin).

- 5 Suitable parasitocidal compounds are those having an aqueous solubility below 100 µg/ml, for example the avermectins and milbemycins. Doramectin is of particular interest (which has an aqueous solubility of 0.6 µg/ml at pH 7). Ivermectin is also of interest.

- 10 Preferably, the bulking agent is lactose. Other suitable bulking agents include other sugars, microcrystalline cellulose (which is available commercially as AVICEL™) and dicalcium phosphate.

- 15 Other tableting excipients which may be present include magnesium stearate, which acts as a lubricant to facilitate tableting. Typically, magnesium stearate will make up about 3% of the implant, by weight. Binding agents may also be included in the formulation to aid granulation and compressibility. Examples of binding agents include starch, gelatin and polyvinyl pyrrolidone. Typically, the binding agent, when present, will make up between 2 to 10% of the implant, by weight.

- 20 A further tableting excipient which the implants of the invention may optionally contain is a tablet disintegrant. Suitable tablet disintegrants include sodium starch glycolate, which is available commercially as EXPLOTAB™. Other disintegrants which may be mentioned are dicalcium phosphate and cross-linked starch. Typically, the disintegrant, when present, will make up about 5% of the implant, by weight.

25

Preferably, the parasitocidal compound (or compounds) makes up between 10 and 60% of the implant, by weight, more preferably from 20 to 45% of the implant, by weight, for example 40%.

- 30 Preferably, the implants of the invention contain an antioxidant or a reducing agent. It has been found that such additives reduce or eliminate degradation of the parasitocidal compound, thus extending the shelf-life of the implant. It has been found that such

additives are particularly useful for stabilizing the parasitocidal compound when the implant is sterilized by irradiation, such as gamma or beta irradiation.

Antioxidants of particular interest are butylated hydroxy anisole (BHA; a mixture of 2-*tert*-butyl-4-methoxyphenol and 3-*tert*-butyl-4-methoxyphenol) and butylated hydroxy toluene (BHT; 2,6-di-*tert*-butyl-4-methylphenol). Other antioxidants and reducing agents include alpha-tocopherol, alkyl gallate derivatives, nordihydroguaiaretic acid, ascorbic acid, sodium metabisulphate and sodium sulphite. Typically, the antioxidant, when present, will make up between 0.01 to 0.5% of the implant, by weight, more preferably 0.1 to 0.2%.

10

As mentioned above, the implants of the invention may be irradiated to sterilize them, typically at a dose in the range 15-25 kGy (kilo Gray).

The implants of the invention may be implanted in various parts of the animal to be treated, for example the flank, the base of the tail or the ear. Where the ears are removed during a meat rendering process, this is a preferred site for implantation.

To facilitate such implantation, the implants are preferably rod-shaped, and can be implanted conveniently using a conventional hand-operated implant gun. Suitably, rod-shaped implants are 2 to 30 mm in length, and 2 to 5 mm in diameter. Preferred dimensions are 5 to 6 mm in length, and 2 to 3 mm in diameter. Preferably, the cross section is circular.

According to the invention, there is also provided a method for the treatment or prevention of parasitic infections which comprises administering an implant as defined above to an animal in need of such treatment.

Parasitic infections of particular interest are those caused by endoparasites including helminthiasis (most frequently caused by nematode worms in the gastrointestinal tract). The implants are also useful in treatment or prevention of ectoparasite infections such as of ticks, mites, lice, fleas, blowfly, biting insects and migrating dipterous larvae.

30

The dosage to be administered will depend on the animal to be treated, the parasitocidal compound being used, and the condition to be treated. However, a suitable dose of doramectin is 0.5 mg/kg of animal body weight. Typically, an implant according to the invention having the preferred dimensions mentioned above will contain about 10 mg of doramectin. Thus, for cattle weighing 120 kg, 6 implants will be needed. This could provide sustained release of doramectin for up to 120 days. Where multiple implants are required, these can often be implanted consecutively by a single actuation of an implant gun.

Because implants according to the present invention can provide sustained release in cattle over an entire grazing season, administration need only take place once a year. Therefore, the invention provides the use of an avermectin or a milbemycin compound in the manufacture of an implant for treatment or prevention of parasitic infections, characterized in that the medicament is administered once a year.

15

The implants of the invention may be prepared by dry- or wet-mass granulation followed by milling and compression into the desired shape using conventional techniques.

For example, an implant consisting of doramectin, lactose and magnesium stearate could be prepared by dry-mass granulation using the following steps:

1. Blend components except magnesium stearate
2. Sieve through a screen
3. Blend
- 25 4. Add half of magnesium stearate
5. Blend
6. Compress into slugs
7. Mill slugs to granules
8. Collect desired size fraction of granules
- 30 9. Blend
10. Add remaining magnesium stearate
11. Blend

12. Compress into rods

The steps for wet-mass granulation are similar, except that some components are sprayed onto other components while they are blending, in a solvent which is later removed. In addition, a binder is used to aid the adherence of the individual particles. For example, in the preparation of an implant containing BHA and the binder PVP, BHA and PVP can be added to a blending mixture of components by spraying as a solution in ethanol. Thus, an implant consisting of doramectin, lactose, sodium starch glycolate, BHA, PVP and magnesium stearate could be prepared by wet-mass granulation using the following steps:

10

1. Blend components except magnesium stearate, BHA and PVP
2. Sieve through a screen
3. Blend
4. Spray solution of BHA and PVP in ethanol onto mixture while mixing
- 15 5. Sieve wet mass
6. Dry to granules
7. Mill
8. Collect desired size fraction
9. Blend
- 20 10. Add magnesium stearate
11. Blend
12. Compress into rods

Thus, according to a further aspect of the invention, there is provided a process for the production of an implant as defined above, which comprises mixing the parasitocidal compound with the tableting excipients and forming into the desired shape.

The duration of action of the implants of the invention may be determined by measuring blood plasma levels in cattle following implantation. These levels have been correlated with antiparasitic activity of the compounds which have established that for effective control of helminths a blood plasma level of about 2 ng/ml needs to be maintained, and that

30

for effective control of single-host ticks a blood plasma level of about 5 ng/ml needs to be maintained.

In a broader aspect, the invention further provides use of an antioxidant or a reducing agent in a composition containing an avermectin or a milbemycin for preventing degradation of the avermectin or milbemycin. Although BHA has been used previously in association with doramectin in DECTOMAX™, its function was to prevent rancidity of the oil formulation rather than to aid the stability of doramectin in solution. This aspect of the invention is particularly useful when the formulation is irradiated, and may be used in liquid and non-liquid formulations (such as solids and powders).

The invention is illustrated by the following examples, and the accompanying figures in which:

Figure 1 shows the blood plasma levels in cattle achieved by the implants prepared in Examples 1 and 2; and

Figure 2 shows the degradation profiles of implants prepared in Example 4.

Example 1

Doramectin implant

Components	Specification	mg/unit	% by weight
Doramectin ^a	Pfizer	10.000	40
β-anhydrous lactose	Ph Eur	14.250	57
Magnesium stearate	Ph Eur	0.750	3
Total		25.000	100

^a mean particle size 19.27 μm (volume mean diameter)

The components, except magnesium stearate, were blended together in a blender for 15 minutes. The blend was then sieved through a 680 μm mesh screen and blended for a further 15 minutes. After that, half of the magnesium stearate was added and blending

continued for 5 minutes, after which the blend was compressed to form "slugs". The slugs were then milled to form granules, and the size fraction 250-355 μm was collected.

- 5 The collected granules were then blended for 15 minutes, and then the remaining half of the magnesium stearate was added and blending continued for 5 minutes. The blend was then compressed on a suitable tablet machine using 2 mm tooling to produce rod-shaped implants of 2 mm diameter and 5 mm length.

Example 2

- 10 Doramectin implant containing a tablet disintegrant

Components	Specification	mg/unit	% by weight
Doramectin ^a	Pfizer	10.000	40
β -anhydrous lactose	Ph Eur	13.000	52
Sodium starch glycolate (EXPLATAB TM)	BP	1.250	5
Magnesium stearate	Ph Eur	0.750	3
Total		25.000	100

^a mean particle size 19.27 μm (volume mean diameter)

- 15 The implants were prepared by the method of Example 1.

Example 3

Pharmacokinetic profiling

- 20 The implants of Examples 1 and 2 were implanted into 16 cows at a dose of 500 $\mu\text{g/kg}$. The blood plasma concentrations of doramectin following implantation were measured, and the results are shown in Figure 1. It can be seen that in each case single-host tick activity was obtained for more than 50 days, and control of helminths was obtained for about 90 days.

Example 4Doramectin implant containing an antioxidant

Components	Specification	mg/unit	% by weight
Doramectin ^a	Pfizer	10.000	40
β -anhydrous lactose	Ph Eur	11.625	46.5
Sodium starch glycolate (EXPLOTAB TM)	BP	1.250	5
Butylated hydroxy anisole	Ph Eur	0.125	0.5
Polyvinyl pyrrolidone	Ph Eur	1.250	5
Magnesium stearate	Ph Eur	0.750	3
Total		25.000	100

- 5 The components, except magnesium stearate, butylated hydroxy anisole and polyvinyl pyrrolidone, were blended together in a blender for 15 minutes. The blend was then sieved through a 680 μ m mesh screen and blended for a further 15 minutes. After that, the butylated hydroxy anisole and polyvinyl pyrrolidone was dissolved in ethanol to form the granulation fluid. The volume of ethanol used was approximately 20%, by volume, of the
- 10 total formulation. The granulation fluid was sprayed onto the blend under constant mixing over 10 minutes. The resultant wet granule mass was sieved through a 1.4 mm mesh screen and allowed to dry under vacuum for 3 hours at 50°C. The dried granules were then milled, and the size fraction 250-355 μ m was collected.
- 15 The collected granules were then blended for 15 minutes, and the magnesium stearate was added and blending continued for a further 5 minutes. The blend was then compressed on a suitable tableting machine using a 2mm tooling to produce rod-shaped implants of 2mm diameter and 5 mm length.
- 20 These implants were used in stability studies, in which the effects of BHA and electron beam irradiation were investigated. Implants containing 0.5% w/w BHA and having been treated at four different irradiation levels [control (0 kGy), 15 kGy, 20 kGy and 25 kGy]

were stored at 30°C for 30 weeks, and then the percentage of doramectin remaining was determined. A control implant containing no BHA was also studied.

The results are shown in Figure 2. It can be seen that the presence of BHA dramatically
5 improves the stability of the implants on storage, even when the implants have been irradiated.

Claims:

1. A solid implant comprising at least one parasitocidal compound having low aqueous solubility; and tableting excipients including a bulking agent.
- 5 2. An implant as claimed in claim 1, which is adapted for subcutaneous implantation.
3. An implant as claimed in claim 1 or claim 2, wherein the parasitocidal compound has an aqueous solubility below 100 µg/ml.
4. An implant as claimed in claim 3, wherein the parasitocidal compound is an avermectin or a milbemycin.
- 10 5. An implant as claimed in claim 4, wherein the parasitocidal compound is doramectin.
6. An implant as claimed in any one of the preceding claims, wherein the bulking agent is lactose.
7. An implant as claimed in any one of the preceding claims, wherein the tableting excipients include magnesium stearate.
- 15 8. An implant as claimed in any one of the preceding claims, wherein the tableting excipients include a tablet disintegrant.
9. An implant as claimed in claim 8, wherein the tablet disintegrant is sodium starch glycolate.
- 20 10. An implant as claimed in any one of the preceding claims, which contains an antioxidant or a reducing agent.
11. An implant as claimed in claim 10, wherein the antioxidant is butylated hydroxy toluene or butylated hydroxy anisole.
12. An implant as claimed in any one of the preceding claims, which is suitable for sterilization, or has been sterilized, by irradiation.
- 25 13. An implant as claimed in any one of the preceding claims, wherein the tableting excipients include polyvinyl pyrrolidone.
14. An implant as claimed in any one of the preceding claims, wherein the parasitocidal compound makes up between 10 and 60% of the implant, by weight.
- 30 15. An implant as claimed in any one of the preceding claims, which is adapted for implantation into the ears of cattle or sheep.
16. An implant as claimed in any one of the preceding claims, which is rod-shaped.

17. Use of an antioxidant or a reducing agent in a formulation containing an avermectin or a milbemycin for preventing degradation of the avermectin or milbemycin.
18. The use as claimed in claim 17, wherein the formulation is suitable for sterilization, or has been sterilized, by irradiation.
- 5 19. The use as claimed in claim 17 or claim 18, wherein the formulation is not liquid.
20. A process for the production of an implant as defined in claim 1, which comprises mixing the parasitocidal compound with the tableting excipients and forming into the desired shape.
21. A method for the treatment or prevention of parasitic infections which comprises
10 administering an implant as defined in any one of claims 1-16 to an animal in need of such treatment.

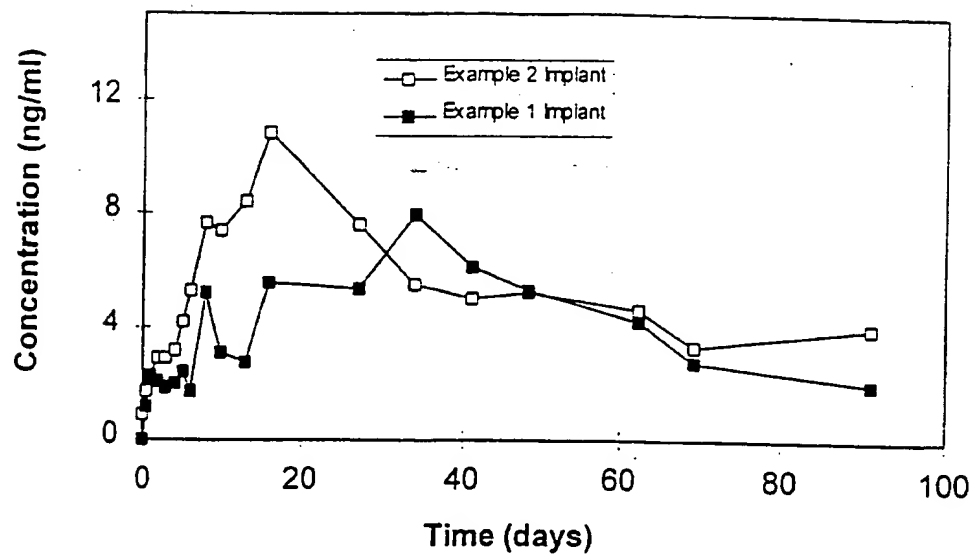


Figure 1

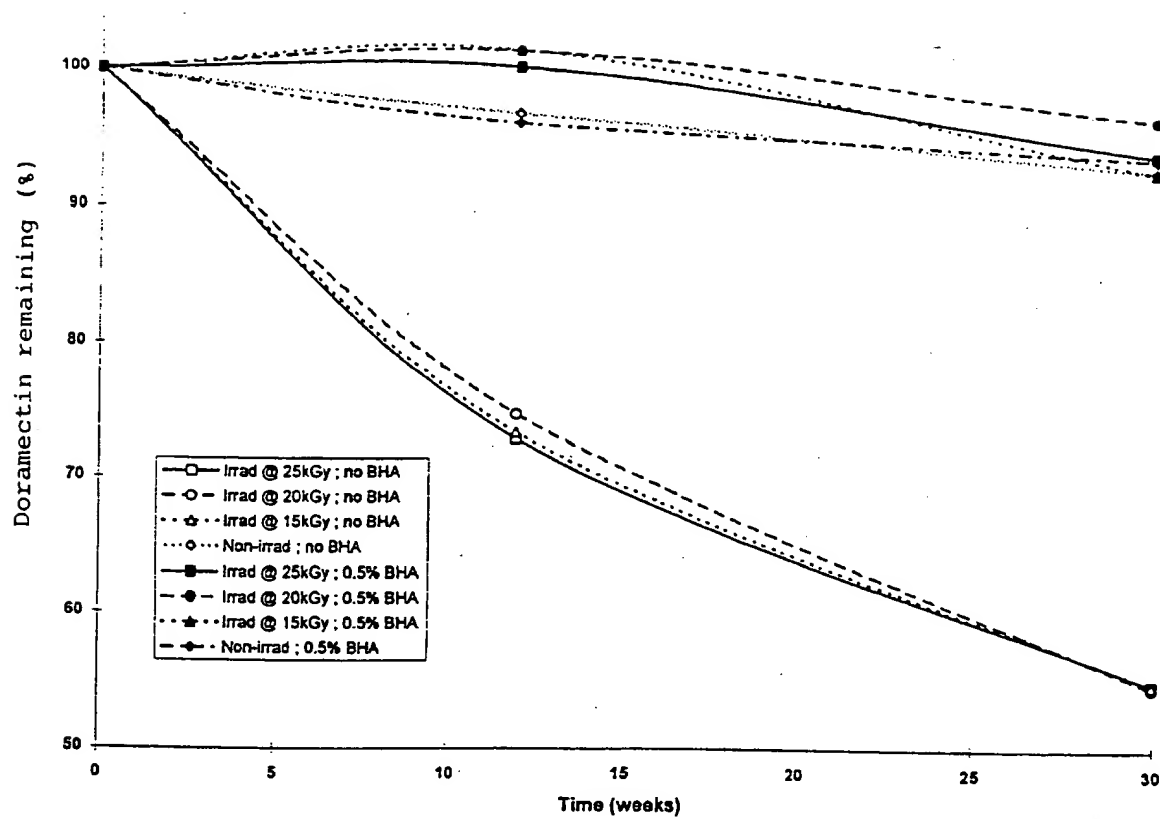


Figure 2

INTERNATIONAL SEARCH REPORT

Inte Application No

PCT/EP 98/05720

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/35 A61K31/365 A61K9/00 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 311 195 A (MERCK) 12 April 1989 cited in the application see claims 1,7,15 ---	1-21
A	EP 0 240 274 A (MERCK) 7 October 1987 cited in the application see claims 1,7 ---	1-21
A	EP 0 473 223 A (MERCK) 4 March 1992 cited in the application see claims 1,3 see examples 7-12 ---	1-21
A	EP 0 537 998 A (MERCK) 21 April 1993 cited in the application see claims 1,7 see page 3, line 2 -----	1-21



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

26 January 1999

Date of mailing of the international search report

02/02/1999

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/05720

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter-Application No

PCT/98/05720

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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